

KIR3DS1-mediated recognition of HLA-*B51: modulation of KIR3DS1 responsiveness by self HLA-B allotypes and effect on NK cell licensing

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Several studies described an association between killer-cell immunoglobulin-like receptor (KIR)/HLA gene combinations and clinical outcomes in various diseases [1-2]. Here, we show that KIR3DS1 mediates positive signals upon recognition of HLA-B*51 (Bw4-I80) surface molecules on target cells and that this activation occurs only in Bw4-I80neg individuals, including those carrying particular KIR/HLA combination settings. In addition, killing of HLA-B*51 transfected target cells mediated by KIR3DS1+/NKG2A+ NK cell clones from Bw4-I80neg donors could be partially inhibited by antibody-mediated masking of KIR3DS1. Interestingly, KIR3DS1-mediated recognition of HLA-B*51 could be better appreciated under experimental conditions in which the function of NKG2D was reduced by mAb-mediated blocking. This experimental approach may mimic the compromised function of NKG2D occurring in certain viral infections. We also show that, in KIR3DS1+/NKG2A+ NK cell clones derived from an HLA-B Bw4-T80 donor carrying 2 *KIR3DS1* gene copy numbers, the positive signal generated by the engagement of KIR3DS1 by HLA-B*51 resulted in a more efficient killing of HLA-B*51-transfected target cells. Finally, we analyzed KIR3DS1+/NKG2A+ NK cell clones from a HLA-B Bw4neg donor carrying cytoplasmic KIR3DL1. Although these clones expressed lower levels of surface KIR3DS1, they displayed responses comparable to those of NK cell clones derived from HLA-B Bw4neg donors that expressed surface KIR3DL1. Altogether these data suggest that, in particular KIR/HLA combinations, KIR3DS1 may play a role in the process of human NK cell education.

References

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- [2] Mancusi et al. (2015) Haploidentical hematopoietic transplantation from KIR ligand-mismatched donors with activating KIRs reduces nonrelapse mortality. *Blood* 125:3173-82.

Keywords

Human NK cells, activating KIRs, KIR3DS1, NK cell education, HLA-B alleles